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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/868,677	10/01/2001	Samuel J. Davis	REG 670A-US	3022
7590 03/17/2004			EXAMINER	
Linda O Palladino Regeneron Pharmaceuticals 777 Old Saw Mill River Road Tarrytown, NY 10591			O HARA, EILEEN B	
			ART UNIT	PAPER NUMBER
			1646	

DATE MAILED: 03/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/868,677

Applicant(s)

DAVIS ET AL.

Examiner

Eileen O'Hara

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 July 2003 and 11 November 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 42-50, 53, 54 and 58-88 is/are pending in the application.
- 4a) Of the above claim(s) 53 and 54 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 42-50 and 58-88 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 42-50, 53, 54 and 58-88 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 42-50, 53, 54 and 58-88 are pending in the instant application. Claims 42, 44, 47, 58 and 71-76 have been amended and claims 51, 52 and 55-57 have been canceled as requested by Applicant in the Paper filed Nov. 28, 2003.

Claims 53 and 54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 42-50 and 58-88 are currently under examination.

Withdrawn Objections and Rejections

2. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Specification

3. The disclosure remains objected to because of the following informalities:

Applicants are advised that the official first page of the specification is the substitute sheet that was entered during prosecution of the PCT application, which had a different priority statement from that of the original first page. In preliminary amendment A, filed October 1, 2001, the amendment to insert the priority information on line 3 resulted in a duplication of some of the priority information, and the retention of the original information, which had an incorrect date. It is recommended that Applicants amend the specification to replace the priority information. Appropriate correction is required.

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Claim Objections

4. Claims 47 and 48 are objected to because of the following informalities: in claims 47 and 48, the word “is” after the second “domain” on the second line of the claims should be replaced with the word “of” to be grammatically correct.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 45-50, 55-58, 62, 68-69 and 71-88 remain rejected and claims 42-44, 51, 52, 59-61, 63-67 and 70 are now rejected under 35 U.S.C. 103(a) as being unpatentable over Pack et al., WO 96/37621, Nov. 28, 1996, and further in view of Davis et al., US Patent No. 6,265,564, filing date Oct. 25, 1996, and further in view of Desnick et al., US Patent No. 5,580,757, Dec. 3, 1996, for reasons of record in the previous Office Action, Paper No. 11, at pages 5-9, and below.

Claims 42-44, 51, 52, 59-61, 63-67 and 70 had been previously rejected under 35 U.S.C. 102(b), but Applicants' amendment have overcome the rejection by canceling claims 51 and 52 and adding the limitation to claims 42 and 71 that the multimerizing component is an immunoglobulin-derived domain, which Pack et al. does not teach.

Claims 42-44, 51, 52, 59-61, 63-67 and 70 are now rejected under 35 U.S.C. 103(a), because it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to make fusion proteins comprising one or more domains of

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receptor binding domains of a ligand or ligands such as angiopoietin-1 and/or angiopoietin-2, either separated by a multimerizing component such as Fc domain of IgG or in tandem, since Pack et al. teach that many receptors can't be activated unless the ligands bind in multimeric form and fusion proteins can be constructed providing these multimeric and more active forms which can be used therapeutically.

Applicants traverse the rejection and assert that Pack et al. teach against the use of immunoglobulin-derived multimerizing domains, and Davis et al. teach fusion proteins that contain only one receptor binding domain of a ligand fused to an Fc domain. Applicants assert that one skilled in the art would not be motivated to combine the references, because Pack et al., teaches away from using immunoglobulin-derived multimerizing domains, and Desnick et al. simply teaches standard host/expression systems and does not cure the defect in Pack et al. or Davis et al., and thus none of the references, either alone or in combination, render the invention *prima facie* obvious.

Applicants' arguments have been fully considered but are not deemed persuasive. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Desnick et al. is not required to cure the deficiencies of Pack and Davis. In response to applicant's arguments against the references individually, one cannot show nonobviousness by

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attacking references individually where the rejections are based on combinations of references.

See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Although Pack et al. discusses the disadvantages of using immunoglobulins as multimerization devices, such as expression of the fusion proteins being restricted to certain expression hosts or the large size of the immunoglobulin domain, Davis et al. constructed fusion proteins comprising domains of the TIE ligands and Fc domain of IgG, and teach that the Fc section of human antibody IgG1 dimerizes upon expression by mammalian cells (column 44, lines 17-34). Davis et al. disclose experiments in which they demonstrate that the monomeric forms of the receptor binding domains do not bind the receptor unless they are joined to an Fc domain, or myc-tag and “clustered” using anti-myc antibodies. Davis et al. also teach that the TIE ligands can only bind in dimeric, trimeric or higher multimeric forms, and that the dimeric form of the fibrinogen-like domain of either TIE-1 or TIE-2 fused to Fc can bind the TIE-2 receptor, whereas monomeric forms cannot (column 18, line 39 to column 19, line 11, column 43, line 40 to column 44, line 60, and Table 1). Use of immunoglobulin domains as multimerizing domains, as taught by Davis et al., have been demonstrated to be effective. The state of the art as a whole is taken into account, even though there may be disparate results in a particular field. Even if some publications teach away from a desired result, those references that teach toward such a result must also be considered, and the state of the art taken as a whole must be considered. In the instant case the positive teachings are not outweighed by the negative teachings. Therefore, the rejection under 35 USC § 103 is maintained.

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It is believed that all pertinent arguments have been answered.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (571) 272-0871.

Official papers Before Final and After Final filed by RightFax should be directed to (703) 872-9306.

The customer service RightFax number is (703) 872-9305.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Eileen B. O'Hara, Ph.D.

Patent Examiner

A handwritten signature in black ink, reading "Lorraine Spector". The signature is written in a cursive, flowing style with a large loop at the beginning and end.

**LORRAINE SPECTOR
PRIMARY EXAMINER**